```
$%^STN;HighlightOn=  ***;Highl[redacted]tOff=***  ;
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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DWPI and DPCI
 NEWS 10  Aug 23  In-process records and more frequent updates now in
                  MEDLINE
 NEWS 11  Aug 23  PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
 NEWS 12  Aug 23  Adis Newsletters (ADISNEWS) now available on STN
 NEWS 13  Sep 17  IMSworld Pharmaceutical Company Directory name change
                  to PHARMASEARCH

 NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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                                                       ENTRY    SESSION
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DICTIONARY FILE UPDATES:  20 SEP 2001  HIGHEST RN 357913-38-3

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Please note that search-term pricing does apply when conducting SmartSELECT sea[redacted]s.

Structure search limits have been increased. See HELP SLIMIT for details.

```
=> e apb/cn
E1            1     APAXIFYLLINE/CN
E2            1     APAZONE/CN
E3            2 --> APB/CN
E4            1     APB (CORROSION INHIBITOR)/CN
E5            1     APB-BMI/CN
E6            1     APBB/CN
E7            1     APBE (PASTEURELLA MULTOCIDA STRAIN IL1403 CLONE PM70 GENE AP
                    BE)/CN
E8            6     APC/CN
E9            1     APC (ACCELERATOR)/CN
E10           1     APC (CAENORHABDITIS ELEGANS GENE EMB-27 SUBUNIT 6)/CN
E11           1     APC (PESTICIDE)/CN
E12           1     APC (PHARMACEUTICAL)/CN

=> s e3
L1            2 APB/CN

=> d l1 1-2

L1   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2001 ACS
RN   139689-20-6  REGISTRY
CN   1H-3-Benzazepine-7,8-diol, 6-bromo-2,3,4,5-tetrahydro-1-phenyl-3-(2-
     propenyl)-, (1R)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-3-Benzazepine-7,8-diol, 6-bromo-2,3,4,5-tetrahydro-1-phenyl-3-(2-
     propenyl)-, (R)-
OTHER NAMES:
CN     ***APB***
FS   STEREOSEARCH
MF   C19 H20 Br N O2
CI   COM
SR   CA
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, TOXLIT
         (*File contains numerically searchable property data)

Absolute stereochemistry.  Rotation (+).

/ Structure 1 in file .gra /

              15 REFERENCES IN FILE CA (1967 TO DATE)
              15 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1   ANSWER 2 OF 2  REGISTRY  COPYRIGHT 2001 ACS
RN   12765-00-3  REGISTRY
CN   APB (corrosion inhibitor) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN     ***APB***
MF   Unspecified
CI   MAN
LC   STN Files:   CA, CAPLUS, TOXLIT

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
               7 REFERENCES IN FILE CA (1967 TO DATE)
               7 REFERENCES IN FILE CAPLUS (1967 TO DATE)


=> e apb domain/cn
E1            2     APB/CN
E2            1     APB (CORROSION INHIBITOR)/CN
E3            0 --> APB DOMAIN/CN
E4            1     APB-BMI/CN
E5            1     APBB/CN
E6            1     APBE (PASTEURELLA MULTOCIDA STRAIN IL1403 CLONE PM70 GENE AP
                    BE)/CN
E7            6     APC/CN
E8            1     APC (ACCELERATOR)/CN
E9            1     APC (CAENORHABDITIS ELEGANS GENE EMB-27 SUBUNIT 6)/CN
E10           1     APC (PESTICIDE)/CN
E11           1     APC (PHARMACEUTICAL)/CN
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E12 1 APC 1/CN

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NEWS 4	Feb 16	TOXLINE no longer being updated
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NEWS 7	May 07	DGENE Reload
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US005912183	41	41	0
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DB Name	Query	Hit Count	Set Name
USPT	l7 near3 benjamin	7	L8
USPT	margolis	993	L7
USPT	l5 not l4	6	L6
USPT	shc same (trk or trka)	11	L5
USPT	shc same (egf or endothelial near1 growth near1 factor)	15	L4
USPT	shc same (her-2 or erbB-2 or cerbB-2 or c-erbB-2 or neu)	2	L3
USPT	apb near5 (domain or recognition)	4	L2
USPT	abp near5 (domain or recognition)	2	L1

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         (c) format only 1999 The Dialog Corp.
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Reexamination, extension, expiration, reinstatement updated weekly.
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         (c) format only 1999 The Dialog Corp.
*File 653: Reassignment data now current through 07/09/99.
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  File 654:US PAT.FULL.  1990-1999/DEC 28
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Set	Items	Description
S1	15	APB(5N)(DOMAIN? OR RECOGNITION?)
S2	8	RD (unique items)
S3	5224	SHC
S4	281	S3(5N)(EGF OR ENDOTHELIAL(W)GROWTH(W)FACTOR)
S5	5	S4(5N)(CANCER OR TUMOR? OR TUMOUR? OR MALIGNAN? OR NEOPLAS? OR CARCINOM?)
S6	2	RD (unique items)
S7	88	S3(5N)(HER OR ERBB OR NEU)
S8	33	RD (unique items)
S9	116	S3(5N)(TRK OR TRKA)
S10	39	RD (unique items)
S11	48	E4,E6

2/7/3 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09996798 BIOSIS NO.: 199598451716
USF binds to the APB-alpha sequence in the promoter of the amyloid beta-protein precursor gene.
AUTHOR: Vostrov Alexander A; Quitschke Wolfgang W; Vidal Frederique; Schwarzman Alexander L; Goldgaber Dmitry(a)
AUTHOR ADDRESS: (a)Dep. Psychiatry Behavioral Sci., State Univ. New York, Stony Brook, NY 11794-8101**USA
JOURNAL: Nucleic Acids Research 23 (14):p2734-2741 1995
ISSN: 0305-1048
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **APB**-alpha **domain** in the amyloid beta-protein precursor (APP) promoter contains a nuclear factor binding domain with the core recognition sequence TCAGCTGAC. Proteins in nuclear extracts from brain and numerous cell lines bind to this domain and it contributes apprx 10-30% to the basal APP promoter activity. Included in this domain is the CANNTG motif, which is recognized by basic helix-loop-helix transcription factors. The same motif is also present in the CDEI element of the yeast centromere and in the adenovirus major late promoter (AdMLP). Here we present evidence based on thermostability, relative binding affinity, electrophoretic mobility and antibody recognition that the cellular proteins that bind to the APB-alpha and CDEI motifs are USF. However, the relative binding affinity for the motifs is different. The affinity of USF for AdMLP is apprx 20-fold higher than for the APB-alpha sequence and 5-fold higher than for the CDEI sequence. Mutational analysis suggested that the primary determinant for USF binding affinity resides within the octamer CAGCTGAC, which is composed of the E-box consensus sequence CANNTG followed by the dinucleotide AC. The human homolog of the mouse CDEI binding protein did not bind to either the CDEI sequence or APB-alpha.

2/7/4 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09435834 BIOSIS NO.: 199497444204
Two nuclear factor binding domains activate expression from the human amyloid beta-protein precursor promoter.
AUTHOR: Quitschke Wolfgang W
AUTHOR ADDRESS: Dep. Psychiatry Behavioral Sci., State Univ. New York, Stony Brook, NY 11794-8101**USA
JOURNAL: Journal of Biological Chemistry 269 (33):p21229-21233 1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Amyloid beta-protein is derived from the amyloid beta-protein precursor (APP), and it is a major component of brain amyloid depositions in Alzheimer's disease and Down's syndrome. Overexpression of APP may be one of several factors contributing to amyloid formation. The APP

promoter was therefore analyzed to determine the mechanism by which APP gene expression is regulated. Cell type-specific expression from the human APP promoter is accomplished with 94 base pairs upstream from the main transcriptional start site. This promoter region contains two nuclear factor binding **domains**, designated **APB**-alpha and **APB**-beta. The contribution of these binding domains to promoter activity was analyzed by transient transfection in HeLa and PC-12 cells. Under standard culture conditions, at least 70-90% of the total activity from the APP promoter can be attributed to binding **domain APB** -beta. The **recognition domain** for this nuclear factor binding site is defined by the sequence GCCGCTAGGGGT (position -93 to -82). The contribution of binding site APB-alpha to APP promoter activity is considerably lower and represents 10-30% of the total activity. The recognition site for the nuclear factor that binds to APB-alpha is delineated by the sequence GGATCAGCTGAC (position -53 to -42). Elimination of both binding sites causes APP promoter activity in vivo to decline to near background levels.

02258023 4319466
The zinc finger protein CTCF binds to the **APB** beta **domain** of the amyloid beta -protein precursor promoter: Evidence for a role in transcriptional activation
Vostrov, A.A.; Quitschke, W.W.
Department of Psychiatry and Behavioral Science, State University of New York, Stony Brook, New York 11794-8101, USA
J. BIOL. CHEM. vol. 272, no. 52, pp. 33353-33359 (1997)
ISSN: 0021-9258
DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Biochemistry Abstracts 2: Nucleic Acids; CSA Neurosciences Abstracts

The promoter of the amyloid beta -protein precursor (APP) gene directs high levels of cell type-specific transcription with 94 base pairs 5' to the main transcriptional start site. An essential activator domain in this proximal APP promoter is a nuclear factor binding site designated as **APB** beta . The **recognition domain** for the **APB** beta binding factor is located between position -93 and -82 relative to the main transcriptional start site. The nuclear factor that binds to the APB beta site was partially purified by multiple steps of ion exchange and hydroxyapatite chromatography. Based on UV cross-linking results, a protein with an apparent molecular mass of 140 kDa was selected as the putative APB beta binding protein. After the final purification step consisting of preparative SDS-polyacrylamide gel electrophoresis, partial peptide sequences were obtained that completely matched the transcriptional factor CTCF. This protein is a known regulator of c-myc and lysozyme gene expression, and it binds to a variety of diverse DNA sequences. The binding of CTCF to the **APB** beta **domain** was further established by competition with CTCF binding oligonucleotides in mobility shift electrophoresis. The identity was also confirmed by the observation that the APB beta binding factor is recognized by antibodies against C- and N-terminal sequences of CTCF. In addition, oligonucleotide competition during in vitro transcription affirmed that CTCF acts as a transcriptional

8/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09360728 BIOSIS NO.: 199497369098
Identification of c-erbB-3 binding sites for phosphatidylinositol 3'-kinase and **SHC** using an EGF receptor/c-**erbB**-3 chimera.
AUTHOR: Prigent Sally A; Gullick William J(a)
AUTHOR ADDRESS: (a)Mol. Oncol. Lab., ICRF Oncol. Group, Hammersmith Hosp., Du Cane Road, London W12 0HS**UK
JOURNAL: EMBO (European Molecular Biology Organization) Journal 13 (12):p 2831-2841 1994
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: c-erbB-3 is a member of the type I (EGF receptor-related) family of growth factor receptors for which no ligand has been identified. To facilitate ligand stimulation we have constructed a chimeric receptor which possesses an activatable kinase and promotes the growth of NIH 3T3 fibroblasts. In this study we have shown that SHC and phosphatidylinositol 3'-kinase bind to the activated EGF receptor/c-erbB-3 chimera. Whereas p85 is not phosphorylated to a significant extent, SHC appears to be a major substrate for phosphorylation on tyrosine. In contrast to EGF receptor and c-erbB-2, we were unable to detect binding of activated c-erbB-3 to GRB2. Using synthetic peptides corresponding to each of 13 potential phosphorylation sites on c-erbB-3, we have shown that tyrosine 1309 is responsible for SHC binding. Peptides containing the motif YXXM inhibit p85 association. By comparison with recently reported SHC binding sites on Middle T antigen and Trk we have identified a SHC binding motif, NPXY.

10/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09611615 BIOSIS NO.: 199598066533
Signaling via the NGF receptor: The **SHC** and CRK proteins associate with **TRK** A in transfected neuronal cells.
AUTHOR: Torres M; Bogenmann E
AUTHOR ADDRESS: Dep. Pediatrics, University Southern Carolifornia, Los Angeles, CA 90027**USA
JOURNAL: Molecular Biology of the Cell 5 (SUPPL.):p265A 1994
CONFERENCE/MEETING: Thirty-fourth Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 10-14, 1994
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English

10/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09596507 BIOSIS NO.: 199598051425
Role of Shc in the activation of Ras in response to epidermal growth factor and nerve growth factor.
AUTHOR: Basu Tanya; Warne Patricia H; Downward Julian(a)
AUTHOR ADDRESS: (a)Imperial Cancer Res. Fund, 44 Lincoln's Inn Fields, London WC2A 3PX**UK
JOURNAL: Oncogene 9 (12):p3483-3491 1994
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Treatment of the rat pheochromocytoma cell tine PC12 with nerve growth factor (NGF) or epidermal growth factor (EGF) is known to result in activation of Ras. In response to EGF treatment, complexes form between Sos, Grb2 and tyrosine phosphorylated Shc and/or EGF receptor. In response to NGF treatment, complexes form between Sos, Grb2 and tyrosine phosphorylated She. While Shc is also found bound to the activated NGF receptor, Trk, no complexes were detectable that contained both Trk and Grb2 or Sos. In streptolysin O permeabilized cells, a tyrosine phosphopeptide, EGFRY1068P, which binds to the SH2 domain of Grb2, totally blocks growth factor induced formation of complexes between Grb2 and Shc or EGF receptor, and also blocks activation of nucleotide exchange on Ras. At low concentrations, another tyrosine phosphopeptide, TRKY490P, which binds to the SH2 domain of She, blocks growth factor induced formation of complexes between **Shc** and the EGF receptor or **Trk**, but fails to block activation of nucleotide exchange on Ras. Higher concentrations of **TRK**-Y490P inhibit tyrosine phosphorylation of **Shc** and the formation of Shc complexes with Grb2: this results in strong inhibition of Ras activation by NGF and partial inhibition of Ras activation by EGF. These data demonstrate that the formation of a trimeric complex between tyrosine phosphorylated Shc, Grb2 and Sos is the key event in the activation of Ras in response to NGF. The binding of Sos to tyrosine phosphorylated receptor, via Grb2 may also contribute to Ras activation by EGF but not NGF, while stable complex formation between Shc and receptors is not necessary for Ras activation by either growth factor.

10/7/18 (Item 18 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09412222 BIOSIS NO.: 199497420592
P75 nerve growth factor receptor modulates p140-trkA kinase activity, but not ligand internalization, in PC12 cells.
AUTHOR: Kahle P; Barker P A; Shooter E M; Hertel Cornelia(a)
AUTHOR ADDRESS: (a)Pharma Div., Preclinical Res., F. Hoffman-La Roche Ltd., CH-4002 Basel**Switzerland
JOURNAL: Journal of Neuroscience Research 38 (5):p599-606 1994
ISSN: 0360-4012
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The biological activity of nerve growth factor (NGF) has been shown to be mediated by the p140-trkA receptor tyrosine kinase, while the role of the p75 NGF receptor (p75-NGFR) is still unresolved. Here we have investigated the relative contribution of p140-trkA and p75-NGFR to early consequences of NGF binding: ligand internalization, p140-**trkA** autophosphorylation, and tyrosine phosphorylation of **Shc**, phospholipase C-gamma-1(PLC-gamma-1), and extracellular signal-regulated kinases (ERKs). It was found that NGF internalization was neither prevented by blocking p140-trkA activity using the protein kinase inhibitors methylthioadenosine, staurosporine, and K-252a, nor by inhibiting NGF binding to p75-NGFR with antibodies. However, when NGF binding to p140-trkA was reduced by the use of a synthetic peptide corresponding to amino acids 36-53 of human p140-trkA, internalization of NGF was decreased. Thus, at least in PC12 cells, internalization appears to require binding of NGF to p140-trkA, but occurs irrespective of p140-trkA kinase activity and ligand occupancy of p75-NGFR. The NGF triple mutant Lys-32/Lys-34/Glu-35 to Ala, which has been demonstrated to bind to p140-trkA, but not to p75-NGFR, induced tyrosine phosphorylation more rapidly than wild-type NGF. Likewise, NGF-induced tyrosine phosphorylation was accelerated when NGF binding to p75-NGFR was prevented with REX-IgG. These findings indicate that NGF binding by p75-NGFR may modulate NGF-induced p14-trkA kinase activity.

10/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09360728 BIOSIS NO.: 199497369098
Identification of c-erbB-3 binding sites for phosphatidylinositol 3'-kinase and SHC using an EGF receptor/c-erbB-3 chimera.
AUTHOR: Prigent Sally A; Gullick William J(a)
AUTHOR ADDRESS: (a)Mol. Oncol. Lab., ICRF Oncol. Group, Hammersmith Hosp., Du Cane Road, London W12 0HS**UK
JOURNAL: EMBO (European Molecular Biology Organization) Journal 13 (12):p 2831-2841 1994
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: c-erbB-3 is a member of the type I (EGF receptor-related) family of growth factor receptors for which no ligand has been identified. To facilitate ligand stimulation we have constructed a chimeric receptor which possesses an activatable kinase and promotes the growth of NIH 3T3 fibroblasts. In this study we have shown that SHC and phosphatidylinositol 3'-kinase bind to the activated EGF

receptor/c-erbB-3 chime[redacted] Whereas p85 is not phosphoryl[redacted]d to a significant exte[redacted] SHC [redacted]ppears to be a major substr[redacted] phosphorylation on tyrosine. In contrast to EGF recep[redacted]r and c-erbB-2, we were unable to detect binding of activated c-erbB-3 to GRB2. Using synthetic peptides corresponding to each of 13 potential phosphorylation sites on c-erbB-3, we have shown that tyrosine 1309 is responsible for SHC binding. Peptides containing the motif YXXM inhibit p85 association. By comparison with recently reported SHC binding sites on Middle T antigen and **Trk** we have identified a **SHC** binding motif, NPXY.

10/7/20 (Item 20 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09308172 BIOSIS NO.: 199497316542
The oncogenic versions of the Ret and **Trk** tyrosine kinases bind **Shc** and Grb2 adaptor proteins.
AUTHOR: Borrello Maria Grazia(a); Pelicci Giuliana; Arighi Elena; De Filippis Lidia; Greco Angela; Bongarzone Italia; Rizzetti Maria Grazia; Pelicci Pier Giuseppe; Pierotti Marco A
AUTHOR ADDRESS: (a)Divisione di Oncologia Sperimentale A, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan**Italy
JOURNAL: Oncogene 9 (6):p1661-1668 1994
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Proto-TRK and proto-RET genes encode receptor type tyrosine kinases. Oncogenic rearrangements of both proto-oncogenes have been detected with a significant frequency in human papillary thyroid carcinomas. Chimeric Ret and Trk oncoproteins, encoded by different rearrangements of proto-TRK and proto-RET genes, display a constitutive phosphorylation on tyrosine. Moreover, it has been shown that phosphorylated tyrosine receptors, activated by their ligands, form multiprotein complexes responsible for transducing mitogenic or differentiation signals. We have therefore begun to analyse in this study the signal transduction pathways triggered by different Ret and Trk oncoproteins. We have shown that the SH2 domain of the adaptor protein Shc coimmunoprecipitates with all the Ret and Trk oncoproteins as well as with NGF-activated proto-Trk receptor. Tyrosine phosphorylation of Trk proteins both normal and oncogenic is necessary for their binding to Shc. In addition, in cells containing either Ret or **Trk** oncoproteins, **Shc** proteins are constitutively phosphorylated on tyrosine and bound to Grb2. Only in in vitro experiments were Ret and Trk oncoproteins shown to bind the SH2 region of Grb2. Finally, when proto-**Trk** product is stimulated by NGF, **Shc** phosphorylation and association with Grb2 are induced. In conclusion, we have shown that Ret and Trk oncoproteins can form multiprotein complexes, however, the functional meaning of the described interactions has to be elucidated.

10/7/21 (Item 21 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09265019 BIOSIS NO.: 199497273389
Neuronal differentiation signals are controlled by nerve growth factor receptor/**Trk** binding sites for **SHC** and PLC-gamma.
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ABSTRACT: Differentiation and survival of neuronal cell types requires the action of neurotrophic polypeptides such as nerve growth factor (NGF). In the central and peripheral nervous system and the pheochromocytoma cell model PC12, NGF exerts its effects through the activation of the signalling capacity of Trk, a receptor tyrosine kinase (RTK) which upon interaction with NGF becomes phosphorylated on tyrosines and thereby acquires the potential to interact with signal-transducing proteins such as phospholipase C-gamma (PLC-gamma), phosphatidylinositol-3'-kinase (PI3'-K) and SHC. Mutagenesis of the specific binding sites for these src homology 2 (SH2) domain-containing substrates within the Trk cytoplasmic domain suggests a non-essential function of PI3'-K and reveals a major role for the signal controlled by the SHC binding site at tyrosine 490 and a co-operative function of the PLC-gamma-mediated pathway for neuronal differentiation of PC12 cells.

10/7/22 (Item 22 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09036936 BIOSIS NO.: 199497045306
Identification of **Trk** binding sites for **SHC** and phosphatidylinositol 3'-kinase and formation of a multimeric signaling complex.
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ABSTRACT: Phosphotyrosine-containing synthetic peptides were used to identify the binding sites for cellular polypeptides involved in nerve growth factor receptor/Trk-mediated signal transduction. In vitro association of SHC and the p85 subunit of phosphatidylinositol 3'-kinase with the Trk tyrosine kinase was prevented only by phosphorylated Y-490- and Y-751-containing peptides, respectively. In spite of the close proximity of the p85 binding site to that of phospholipase C-gamma (Y-785), both target proteins are able to interact with the same receptor molecule simultaneously.

10/7/28 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

05694446 EMBASE No: 1994106681
Trk receptors use redundant signal transduction pathways involving SHC and PLC-gamma1 to mediate NGF responses
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In response to NGF, the Trk receptor tyrosine kinase forms a complex with SHC, a protein that couples receptor tyrosine kinases to p21(ras). Complex formation between **Trk** and **SHC**, **SHC** tyrosine phosphorylation, and association of SHC with Grb2 were mediated by autophosphorylation at V490 in Trk (NPQYFSD). To determine the role of **SHC** and other **Trk** substrates in NGF signaling, Trk receptors with mutations in Y490 and Y785 (the PLC-gamma1 association site) were introduced into PC12nnr5 cells. NGF treatment of PC12nnr5 cells expressing Trk with mutations in either substrate-binding site resulted in normal neurite outgrowth and Erk1 activity and tyrosine phosphorylation. However, PC12nnr5 cells expressing Trk with mutations at both sites failed to stably extend neurites and efficiently induce Erk1 activity and tyrosine phosphorylation in response to NGF. We postulate that Trk receptors can activate Erk1 by either SHC- or PLC-gamma1-dependent signaling pathways. These results suggest a model whereby Trk receptors utilize at least

10/7/33 (Item 3 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

01826486 3610423
P75 nerve growth factor receptor modulates p140 super(trkA) kinase activity, but not ligand internalization, in PC12 cells
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SUBFILE: CSA Neurosciences Abstracts

The biological activity of nerve growth factor (NGF) has been shown to be mediated by the p140 super(trkA) receptor tyrosine kinase, while the role of the p75 NGF receptor (p75 super(NGFR)) is still unresolved. Here we have investigated the relative contribution of p140 super(trkA) and p75 super(NGFR) to early consequences of NGF binding: ligand internalization, p140 super(**trkA**) autophosphorylation, and tyrosine phosphorylation of **Shc**, phospholipase C sub(gamma -1) (PLC sub(gamma -1)), and extracellular signal-regulated kinases (ERKs). It was found that NGF internalization was neither prevented by blocking p140 super(trkA) activity using the protein kinase inhibitors methylthioadenosine, staurosporine, and K-252a, nor by inhibiting NGF binding to p75 super(NGFR) with antibodies. The findings indicate that NGF binding by p75 super(NGFR) may modulate NGF-induced p140 super(trkA) kinase activity.